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Disease-a-Month

Hypoglycemia

GERALD T. PERKOFF
FRANK H. TYLER

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Hypoglycemia

GERALD T. PERKOFF
FRANK H. TYLER

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IN THE 35 YEARS that have elapsed since Harris described the characteristic clinical symptoms associated with spontaneous decreases in blood glucose (18), hypoglycemia has been demonstrated in a variety of clinical situations. The purpose of this paper is to present an approach to the problem of hypoglycemia based on recent advances in the understanding of carbohydrate metabolism. No attempt will be made to discuss each of the many causes of hypoglycemia, but the few common types will be described together with representative cases. In addition, some of the rare causes of hypoglycemia will be discussed in detail in the hope of clarifying certain basic physiologic processes of general interest. We—and physicians in general—owe a debt of gratitude to Dr. Jerome Conn, whose pioneer work in this field (10) is the basis

for any presentation of the subject of hypoglycemia. The reader is referred to Dr. Conn's many papers for detailed etiologic and clinical descriptions of the various types of hypoglycemia.

FACTORS INFLUENCING NORMAL BLOOD GLUCOSE LEVEL

The normal blood glucose level represents a balance between several endocrine and nonendocrine factors, some of which change the rate at which glucose enters the blood stream while others change the rate at which glucose leaves the blood stream. A number of the factors which are most important in the regulation of blood glucose levels affect both phenomena.

Insulin is the single most important substance involved in the regulation of the blood glucose. This hormone is a protein which is secreted by the β-cells of the islets of Langerhans in response to changes in blood glucose level. Under normal circumstances, maximal blood levels of insulin are found 1 to 2 hours after carbohydrate ingestion. The maximal rise in blood insulin after eating occurs at about the time the blood glucose level returns to normal.

The blood glucose lowering effect of insulin has been studied intensively for many years, and the mechanism of action of insulin is now partially understood. Levine *et al.* (23), in a series of carefully conducted experiments, have shown that insulin is capable of increasing the volume of body fluid in which sugars resembling glucose are distributed from that of extracellular fluid to that of total body water. This action, which is preceded by the binding of the insulin molecule to muscle (34), is at least partially specific for sugars with the same spacial configuration about carbon atoms 1, 2 and 3 as glucose. These observations suggest that the major action of insulin is to increase the rate of transfer of free glucose from the extracellular space to the cell. Exactly how insulin brings about this change in the distribution of glucose is unknown. In association with the binding of insulin, the physical state of the cell membrane may change to allow diffusion of glucose through the membrane, or insulin may cause a change in the activity of the hypothetical "glucose transferase" enzyme system. Since it now has been shown that free glucose is present within the cell (29), it no longer seems likely that the action of insulin is mediated through the phosphorylating enzyme, hexokinase. Almost

all the secondary effects of insulin on intermediary metabolism, such as lipogenesis, nitrogen storage, carbon dioxide production, and so forth, can be considered to be a direct result of the increase in intracellular free glucose concentration.

Most of the studies of the action of insulin have been made in eviscerated animals and in isolated muscle tissue. The effects of insulin described above can be said to obtain with certainty in muscle, the major peripheral site of glucose metabolism. An influence of insulin on the liver has been less certain, but evidence which helps to resolve the controversies about this point has been obtained recently. For some time, it has been known that insulin causes a sharp decrease in glucose production by the liver in vivo (3), but many workers have experienced difficulty in demonstrating reproducible effects of insulin on liver tissue in vitro. However, it has been observed that insulin administered via the portal vein has effects different from those obtained when it is given by the peripheral venous route (24). Intraportal doses of insulin which are too small to result in increased peripheral utilization of glucose still cause a profound decrease in hepatic glucose output. This suggests that endogenous insulin, if secreted into the portal bed in amounts sufficient to raise the peripheral venous insulin level, would result both in decreased hepatic glucose outflow and in increased transfer of glucose into peripheral muscle cells. Thus, insulin could change both the rate of entry of glucose into and the egress of glucose from the blood stream.

Epinephrine, another important material in the regulation of the normal blood glucose level, increases the blood glucose in two ways. The primary action of epinephrine is to increase the rate of hepatic glycogenolysis by potentiating phosphorylase activity (36). This causes cleavage of the glucose-phosphate bonds and results in increased hepatic glucose production. A secondary effect of epinephrine is to decrease the peripheral utilization of glucose. This effect is best demonstrated by the measurment of the arteriovenous glucose difference. After epinephrine administration, the arteriovenous glucose difference approaches zero (33). Epinephrine, therefore, increases the rate of glucose entry into blood and slows its rate of egress from the blood stream.

Glucagon, a polypeptide which has certain actions similar to both epinephrine and insulin, has been subjected to intensive

study in recent years. Although the site of origin of glucagon is uncertain, most likely this substance is formed and secreted by the α-cells of the islets of Langerhans. The major action of glucagon is to increase blood glucose levels by increasing hepatic glycogenolysis (36). The mechanism of this action is the same as that of epinephrine. A second effect of glucagon is to *increase* the peripheral uptake of glucose by the tissues. In contrast to epinephrine, glucagon causes an increased arteriovenous blood glucose difference (12). It has been postulated that glucagon may function as a rapidly acting emergency substance to increase blood glucose and to aid in its entry into cells. Nevertheless, although one can postulate a function for glucagon in the regulation of carbohydrate metabolism, there is no definitive evidence that this material is a physiologic hormone in man.

Hydrocortisone, the 17-hydroxycorticosteroid produced by the adrenal cortex, plays a major role in the maintenance of blood glucose. The principal action of hydrocortisone on carbohydrate metabolism is to increase gluconeogenesis, the conversion of non-carbohydrate substances to carbohydrate. This results in an increase in liver glycogen. The exact mechanism by which hydrocortisone exerts this effect is unknown, but it has been suggested that the steroid blocks the entry of pyruvate into the Krebs cycle, with a resultant increase in the metabolic pool of active 1, 2 and 3 carbon compounds, which are then converted to glucose (16). A second effect of hydrocortisone is to decrease the rate at which glucose is cleared from the plasma. Whether this is accomplished by inhibition of the hexokinase reaction or in some other way is not known.

Thyroxine, too, affects glucose levels in two ways, although its importance in the over-all maintenance of blood glucose levels is much less than is that of hydrocortisone. Thyroxine increases the rate of glucose removal from plasma and also decreases liver glycogen. Both of these effects are thought to be secondary to the increased metabolic rate rather than being due to primary effects on carbohydrate metabolism per se.

The role of pituitary secretions in the maintenance of blood glucose levels is still in doubt. Hypophysectomized animals, including man, are exquisitely sensitive to insulin, but this is due in part to the adrenal atrophy which accompanies the cessation of ACTH

secretion. However, the best primate growth hormone preparations, including highly purified human growth hormone, have been shown to have hyperglycemic properties in man. Presumably, then, this material exerts an effect on blood glucose levels in some way, but the exact mechanism is not known.

That exercise can lower blood glucose levels in man has been suspected for many years, but adequate proof of this fact has only recently been forthcoming. Christophe and Mayer (7) have shown that graded exercise increases the rate of removal of glucose from the blood in a predictable fashion. We have made similar observations in our laboratory. The mechanism of this effect is not completely understood, but some information concerning the way in which muscular activity affects blood glucose levels is available. Goldstein *et al.* (17) have shown that exercise increases the volume of glucose distribution in eviscerated animals to a degree similar to that found with insulin administration. This change occurs in the absence of the pancreas, and can occur in the recipient animal of a cross-circulated pair when only the donor animal is exercised. It is postulated that a noninsulin humoral agent released from muscle during exercise causes the observed changes.

It is of interest that carbohydrate ingestion, although resulting in sharp increases of blood glucose level and liver glycogen, has little over-all effect on blood glucose maintenance. During starvation, an initial small decrease in blood glucose is observed, but this value then becomes stabilized and remains essentially unchanged for long periods thereafter (21). Apparently the process of gluconeogenesis coupled with essential cessation of insulin secretion during starvation suffices to maintain a normal blood glucose level.

PATHOLOGIC PHYSIOLOGY OF HYPOGLYCEMIA

From a consideration of the factors responsible for maintaining a normal blood glucose level, it is clear that hypoglycemia can occur in several ways. An abnormally rapid rate of clearance of glucose from the plasma, with decreased hepatic glucose production is responsible for the hypoglycemia associated with an

excessive amount of insulin, whether this be of endogenous or exogenous origin. Diminished gluconeogenesis, with resultant inadequate hepatic glycogen stores and diminished hepatic glucose output, is the major factor responsible for the hypoglycemia of primary adrenal insufficiency and panhypopituitarism.

Failure of end-organ response to normal regulating mechanisms is the most probable cause of hypoglycemia in liver disease. Decreased glycogen stores may contribute to the low blood glucose levels occasionally found in this circumstance. A classic example of failure of end-organ response which leads to hypoglycemia is that of glycogenosis (von Gierke's disease). In this disorder, excessive glycogen storage occurs in the liver and elsewhere because of the absence of glucose-6-phosphatase. This leads to failure of glycogenolysis even though the glycogen concentration in the liver is high and the carbohydrate regulating factors are normal.

In certain clinical circumstances, the demand for glucose in the peripheral tissues is so great that hypoglycemia may result. This is the mechanism of the hypoglycemia which occurs, occasionally, with extreme exercise, as well as in some cases of thyrotoxicosis. In the latter instance, decreased liver glycogen stores may also contribute to the hypoglycemia. Excessive utilization of glucose in a specific peripheral tissue also is the probable mechanism producing low blood glucose levels in some of the reported instances of hypoglycemia occurring with massive fibrous tumors (30).

The physiology of hypoglycemia in some other situations is less well understood than in those already mentioned. These are circumstances in which isolated genetic metabolic abnormalities have occurred and are unexplained at present. Examples of this type of hypoglycemia include familial hypoglycemia following the ingestion of specific amino acids (8) and idiopathic hypoglycemosis of infancy (25).

There are still other theoretical mechanisms for hypoglycemia which have as yet not been observed in patients. Diminished insulin destruction by hepatic insulinase and increased sensitivity of the peripheral tissues to insulin action can be included as examples here.

CLASSIFICATION OF THE HYPOGLYCEMIAS

The foregoing considerations of the possible physiologic mechanisms for the production of hypoglycemia lend themselves well to a classification of the hypoglycemias. It is useful, however, to supplement such a physiologic classification by subdividing hypoglycemias as "organic" or "functional." As presently understood, these terms are used to indicate the presence of demonstrable metabolic disease of the major organs responsible for the regulation of carbohydrate metabolism (organic) or the absence of such disease of these organs (functional). These terms are not correct in a strict sense. A hypoglycemia classified as organic, such as that occurring in adrenal insufficiency, ultimately results from a lack of liver glycogen—a functional change. Similarly, a type of functional hypoglycemia occurs in some instances of encephalitis, presumably due to derangement of central control of insulin secretion. Although there is underlying organic brain disease, the hypoglycemia is related to altered function of the insulin-secreting mechanism, and therefore has the characteristics of functional hypoglycemia. Nevertheless, despite such objections to the classification of hypoglycemias as functional and organic, the subdivision is useful because hypoglycemia responsiveness (the ability of the body to raise the blood glucose in response to low glucose levels) is normal in functional hypoglycemia and grossly impaired in all types of organic hypoglycemia.

Since the demonstration of the presence or absence of hypoglycemia responsiveness is the keystone in the differentiation of the type of hypoglycemia, it will be profitable to consider this phenomenon. When insulin is administered intravenously to a normal person, the blood glucose decreases promptly and reaches a nadir in 20–30 minutes. After this time, the blood glucose level rises and usually has returned to the fasting level within 90 minutes. The process by which the blood glucose is restored to normal is called the response to hypoglycemia or hypoglycemia responsiveness. In the individual patient, the identification of the type of response to hypoglycemia is the single most important procedure in the differentiation of functional from organic hypoglycemia. In the former, hypoglycemia responsiveness is present and normal; in the latter, it is absent or greatly decreased (hypoglycemia unresponsiveness).

The mechanism of hypoglycemia responsiveness is not well understood. When it became known that the administration of epinephrine or glucagon resulted in prompt increases of blood glucose levels, it was assumed that one or both of these compounds might be secreted in response to insulin hypoglycemia and could be the factors responsible for raising the blood glucose. Unfortunately, definitive studies of this phenomenon cannot be carried out in man. However, even in adrenalectomized, pancreatectomized and hypophysectomized animals (22), hypoglycemia responsiveness is normal as long as adequate liver glycogen is present. This suggests that hypoglycemia responsiveness depends on hepatic glycogenolysis induced by the low blood glucose level per se, just as insulin secretion is thought to occur in direct response to elevation of the blood glucose level.

In adrenal or pituitary insufficiency, hypoglycemia unresponsiveness is due to lack of liver glycogen. In glycogenosis, abnormality of the enzymatic mechanisms responsible for glycogenolysis explains the presence of hypoglycemia unresponsiveness in the face of adequate glycogen stores.

As stated earlier, the major action of insulin is to increase glucose entry into the cell, which theoretically should result in increased liver glycogen and normal hypoglycemia responsiveness. Nevertheless, despite the fact that the liver glycogen content is increased above normal, response to hypoglycemia is absent in patients with islet cell adenoma of the pancreas. An explanation of this apparent contradiction is found, first, in the fact that insulin causes a marked decrease in glucose-6-phosphatase activity in liver (1). Since this enzyme is responsible for the release of glucose into the blood stream, a decrease in its activity would diminish the liver's ability to respond to hypoglycemia. Second, preliminary observations in our laboratory suggest that prolonged insulin action may result in decrease in the concentration of that form of glycogen which is readily available for conversion to glucose.

Regardless of which mechanism for hypoglycemia unresponsiveness is operative, it must be emphasized that demonstration of the presence of this phenomenon effectively excludes functional hypoglycemia.

By first subdividing the hypoglycemias into organic and functional groups, and then separating these disorders according to the

physiologic basis for their occurrence, a useful classification can be devised. It should be noted that some rare types of hypoglycemia have not been included (10).

I. *Organic hypoglycemia:*
  A. Increased removal of glucose from, and decreased entry of glucose into, blood
    1. Islet cell adenoma
      (a) Benign
      (b) Malignant
    2. Hyperplasia of the islets of Langerhans
    3. Self-administration of insulin
  B. Decreased rate of entry of glucose into blood
    1. Due to failure of end-organ response
      (a) Glycogenosis (von Gierke's disease)
      (b) Various kinds of hepatic disease
    2. Due to insufficient hepatic glycogen
      (a) Primary adrenal insufficiency
      (b) Panhypopituitarism
      (c) Some instances of hepatic disease
  C. Increased rate of glucose removal from the blood
    1. Massive fibrous tumors
    2. Thyrotoxicosis
  D. Due to genetic metabolic abnormality of unknown type
    1. Idiopathic hypoglycemosis
    2. Familial sensitivity to amino acids
  E. Theoretical causes
    1. Decreased destruction of insulin
    2. Increased sensitivity of tissues to insulin

II. *Functional hypoglycemia:*
  A. Due to increased removal of glucose from, and decreased entry of glucose into, blood
    1. Spontaneous functional hypoglycemia
      (a) Associated with anxiety
      (b) Associated with central nervous system disease
    2. Hypoglycemia of early diabetes mellitus
    3. Alimentary hyperinsulinism
  B. Due to increased rate of removal of glucose from blood —severe exercise

RECOGNITION OF HYPOGLYCEMIA

The recognition of hypoglycemia depends on awareness of the fact that a wide variety of recurrent symptoms can be the result of low blood glucose levels. The group of symptoms commonly thought to be characteristic of hypoglycemia, such as sweating, tremulousness, hunger and tachycardia, actually account for only a few of the presenting complaints of patients with low blood glucose levels. These occur primarily in situations such as functional hypoglycemia where the blood glucose level decreases rapidly. Although such symptoms may occur in sympathectomized patients, they are thought to be due to the compensatory secretion of epinephrine in response to the low blood glucose and not to the actual glucose level itself.

Persistent hypoglycemia of slower onset, characteristic of the various forms of organic hypoglycemia, more frequently yields symptoms directly attributable to the effects of the low blood glucose on cerebral function. In this group of abnormalities, progressive degrees of cerebral depression are correlated with increasing severity of hypoglycemia. The symptoms include headache, nausea, visual and speech disturbances, personality aberrations, grossly psychotic behavior, various neurologic abnormalities, convulsions and coma. The gamut of clinical signs and symptoms may be so varied as to suggest the presence of serious neurologic or psychiatric disease. An additional confusing aspect of the clinical picture of hypoglycemia stems from the fact that hypoglycemia may result in actual brain damage. Abnormal neurologic signs, therefore, may persist after the blood glucose level has returned to normal.

Certain points in the history are helpful in suspecting hypoglycemia in patients with unusual complaints. First, recurrence of symptoms during the night or early morning is typical of organic hypoglycemia. This type of hypoglycemia, with its relatively slow onset and abnormal hypoglycemia responsiveness, is exaggerated greatly by fasting, and usually is relieved by meals. Functional hypoglycemia does not occur on fasting, but follows carbohydrate ingestion. In this latter group, therefore, the periodicity of complaints bears a relationship to eating, with attacks usually occurring 1–3 hours after meals.

When hypoglycemia is suspected, proof of the presence and significance of this abnormality rests on the demonstration of a low blood glucose level at the time the symptoms occur, and on the prompt relief of symptoms after the administration of glucose. In organic hypoglycemia, it usually is possible to demonstrate the low blood glucose during a spontaneous attack, since the hypoglycemia is persistent and hypoglycemia unresponsiveness is present. In functional hypoglycemia, on the other hand, the response to the hypoglycemia may be so prompt that blood cannot be drawn for glucose determination before the level has risen to normal. In such patients, it is necessary to induce hypoglycemia by artificial means to show that the patient's symptoms are, indeed, hypoglycemic in origin.

Hypoglycemia per se is a sign of disease, just as anemia is a sign of disease, and not a disease in itself. The demonstration that a patient's symptoms are the result of hypoglycemia is merely the first step in the recognition of the underlying disorder responsible for the low blood glucose level.

CARBOHYDRATE METABOLISM TESTS IN HYPOGLYCEMIA

In addition to the standard clinical procedures for the recognition of hepatic, adrenal and pituitary disease, the differential diagnosis of the type of hypoglycemia can be made best by use of several tests of carbohydrate metabolism. The most valuable tests are the standard oral glucose tolerance test, the intravenous glucose tolerance test, the intravenous insulin tolerance test and the effects of prolonged fasting.

Blood Glucose Methods

Since the absolute values obtained when blood glucose levels are measured depend on the analytical methods used, some attention must be given to commonly used technics for glucose determination. These are of three types: (1) those involving measurement of reducing substances in blood after protein precipitation with barium hydroxide and zinc sulfate; (2) those utilizing other blood protein precipitants, principally sodium tungstate-sulfuric acid and (3) those dependent on specific glucose oxidation by the enzyme, glucose oxidase. The values obtained by the barium-zinc

precipitation methods represent reducing sugars in blood, primarily glucose. Fructose, pentoses and noncarbohydrate reducing substances will be measured, however, if they are present in the filtrate. The latter are essentially all removed by the zinc hydroxide precipitation procedure. The best example of this type of method is that of Nelson-Somogyi (27), which gives a normal range of blood glucose from 50 to 90 mg./100 ml. This is the procedure we have found most useful.

Values obtained with other precipitation methods represent reducing sugars in blood plus some noncarbohydrate reducing substances. The major method of this type is that of Folin (14), using a sodium tungstate precipitation. This method is usually called the Folin-Wu method, since Wu was responsible for popularization of the tungstate filtrate. Normal values range from 80 to 110 mg./100 ml. It is evident that a blood glucose level of 60 mg./100 ml. would represent hypoglycemia if this method were used, but would be a normal value by the Nelson-Somogyi technic.

More recently, blood glucose has been measured specifically with glucose oxidase. This technic, however, is more difficult than either of the other two and is used primarily for research purposes.

Glucose Tolerance Tests

Several important points must be kept in mind when glucose tolerance tests are used in the study of the hypoglycemic patient. A glucose tolerance test does not merely distinguish the diabetic from the nondiabetic subject. After a standard dose of glucose, the blood glucose rises from fasting levels of 60–70 mg./100 ml. (Nelson-Somogyi) to 120–140 mg./100 ml. in 1 hour. Normally, the blood glucose begins to fall during the period from 30 to 90 minutes after glucose ingestion, while glucose absorption continues. This is due to peripheral utilization and hepatic storage of glucose and relates in part to insulin secretion. The blood glucose level usually is normal within 2 hours and drops below normal as absorption ceases and insulin action continues. The response to hypoglycemia then occurs, and the blood glucose level becomes normal. The initial rise in blood glucose indicates adequate absorption from the gastrointestinal tract. In certain circumstances (alimentary hyperinsulinism), the rapidity and degree of blood glucose rise is of diagnostic aid; the blood glucose decrease gives

some measure of the state of the insulin-secreting mechanism. To corroborate the diagnosis of hypoglycemia, the nadir must be observed carefully, and the test must be continued for a longer period than when the diagnosis in question is diabetes mellitus. In the study of the hypoglycemic patient, the test must be continued for at least 5 hours because the onset of hypoglycemia and the identification of the presence or absence of hypoglycemia responsiveness may be delayed for this period.

With reference to oral tolerance tests, it is important to recognize that a significant proportion of normal subjects have a flat oral glucose tolerance curve. Tests of this type have little diagnostic significance. Specifically in relation to hypoglycemia, if the blood glucose level fails to rise, insulin secretion of the degree necessary to produce hypoglycemia is not produced. It is apparent that to be of value in the study of a patient with hypoglycemia, the test used actually must produce low blood glucose levels, so that hypoglycemia responsiveness may be evaluated. Even in adrenal and pituitary insufficiency, where flat oral glucose tolerance curves are characteristic, this finding is of little diagnostic aid because of the frequency of occurrence of flat curves in the general population.

In some respects, the intravenous glucose tolerance test is superior to the oral test. Flat curves are avoided and the blood glucose regularly is raised to levels sufficient to stimulate insulin secretion. Therefore, hypoglycemia responsiveness can be tested more adequately.

Irrespective of the type of glucose tolerance test that is used, adequate dietary preparation of the patient is essential (10). Many of the vagaries of glucose tolerance tests can be eliminated by the ingestion of a diet containing at least 300 Gm. of carbohydrate for 3 days before the test is performed. In this way, prolonged elevations of blood glucose due to carbohydrate starvation can be prevented and the shape of the curve becomes diagnostically valuable. Particularly in the demonstration of hypoglycemia responsiveness it is essential that artifactual prolongation of hyperglycemia be avoided and that adequate hepatic glycogen stores be present.

PROCEDURE FOR ORAL GLUCOSE TOLERANCE TEST.—The test is carried out after standard dietary preparation. After a fasting

specimen has been drawn for determination of blood glucose, 100 Gm. of glucose (1.75 Gm./kg. body weight for children), dissolved in water and flavored with lemon juice, is administered orally. Blood samples are drawn for glucose analysis at ½, 1, 2, 3, 4 and 5 hours after the ingestion of glucose. Although the use

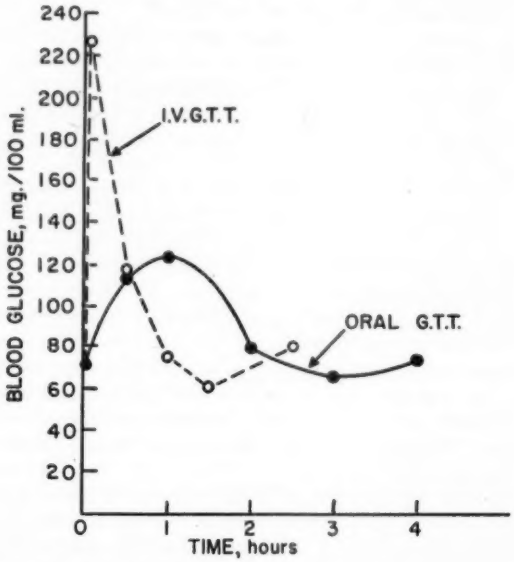

FIG. 1.—Normal oral and intravenous glucose tolerance tests.

of capillary blood has been recommended for the glucose determinations, we have found venous blood satisfactory. A normal curve is shown in Figure 1.

PROCEDURE FOR INTRAVENOUS GLUCOSE TOLERANCE TEST.—This test can be performed in several ways. For any of them, the patient is prepared in the same manner as for the oral test. A procedure we have found satisfactory is to give 25 Gm. (or 0.5

Gm./kg.) of glucose by injection over 1–2 minutes after the fasting blood sample has been drawn. Blood samples are taken 5 minutes after the end of the injection, and at ½, 1, 1½, 2, 2½, 3 and 3½ hours after the injection. An alternative procedure is useful in some patients in whom glucose is removed from the plasma at an excessive rate. Instead of waiting 30 minutes for the second blood sample, multiple samples of blood are drawn at 5-minute intervals for 30 minutes, and further sampling then is carried out at 30-minute intervals for 3 hours. When the glucose values are plotted logarithmically, the rate of disappearance of glucose from the plasma can be calculated, and the excessively rapid decrease in blood glucose level demonstrated. In addition, the decrease in glucose disappearance rate with increasing age can be demonstrated by this means (32). Recognition of this age change in glucose tolerance provides a further explanation for variations in glucose tolerance tests reported previously when this factor was not considered, and adds to the value of this test as a standard procedure. In addition, the effect of insulin in accelerating glucose removal is clearly shown by giving a small dose of intravenous insulin with the glucose injection. A normal intravenous glucose tolerance curve is shown in Figure 1.

Insulin Tolerance Tests

Many workers do not use the insulin tolerance test in the study of the hypoglycemias because of the frequent occurrence of inconsistent results. However, these variations can be eliminated by the use of a standardized procedure. There are several sources of error in the use of the insulin tolerance test. First, only an intravenous insulin tolerance test can be used. Because of variations in the absorption of insulin, subcutaneous insulin tolerance tests give variable results. The subcutaneous administration of insulin has been responsible for many of the unsatisfactory results reported with insulin tolerance tests.

A second important reason for the fact that many workers have discarded the insulin tolerance test is that they have attempted to

use it as a measure of insulin "sensitivity." As originally described (15), a normal insulin tolerance test was stated to be characterized by a 50% decrease of blood glucose level from fasting, and by a nadir reached at 30 minutes. Decreases greater than 50%, reaching a nadir more rapidly than 30 minutes, were considered abnormal. Many physicians have assumed, incorrectly, that these more dramatic changes represent increased "sensitivity" to insulin. In our laboratory, intravenous insulin tolerance tests in normal subjects frequently have revealed blood glucose levels of 5–15 mg./100 ml., with the nadir occurring as early as 20 minutes after insulin injection. It is apparent, therefore, that these changes cannot be considered to be outside the range of normal. While it is true that in certain situations blood glucose levels do fall more rapidly than normal after insulin administration, the insulin tolerance test cannot be used to demonstrate this phenomenon. The small magnitude of the blood glucose changes possible in this test, coupled with relatively infrequent sampling, precludes obtaining valid measurements of the disappearance of glucose. The effect of insulin on glucose removal ("sensitivity") can be evaluated, but this must be done with rapid multiple sampling of venous blood during the first hour of an intravenous glucose-insulin tolerance test, followed by semilogarithmic graphing of the values and careful calculation of the rate of decrease of glucose concentration (32). The insulin tolerance test should not be used in patients in whom there is strong suspicion of adrenal or pituitary insufficiency. Because of the severe hypoglycemia unresponsiveness present in these disorders, irreversible hypoglycemia may occur under these circumstances.

Finally, although not as critical here as with the glucose tolerance test, adequate dietary preparation is useful to insure consistent results.

PROCEDURE FOR INSULIN TOLERANCE TEST.—The patient is studied fasting in the postabsorptive state. After drawing the fasting blood sample, crystalline or regular insulin, 0.1 units per kg. body weight, is administered intravenously. Blood samples are

drawn at 10, 20, 30, 40, 50, 60 and 90 minutes. A syringe containing 50% glucose solution should be available for prompt termination of the test if a severe hypoglycemic reaction occurs. Most normal patients will complain of sweating, tremulousness and hunger beginning 20–40 minutes after the insulin has been given. These symptoms then subside rapidly. Prolonged persistence of symptoms, or the occurrence of progressive evidence of hypoglycemia, requires termination of the test. It is desirable, however, to continue the test until enough time has elapsed to demonstrate the normal response to hypoglycemia or the presence of hypoglycemia unresponsiveness. Hypoglycemia responsiveness can be considered to be normal if the blood glucose concentration has returned to or near normal by the 90-minute sample. A normal curve is shown in Figure 2. It is apparent that hypoglycemia responsiveness is well demonstrated with the insulin tolerance test. The glucose tolerance tests shown in Figure 1, while they show hypoglycemia responsiveness, are less adequate for this purpose.

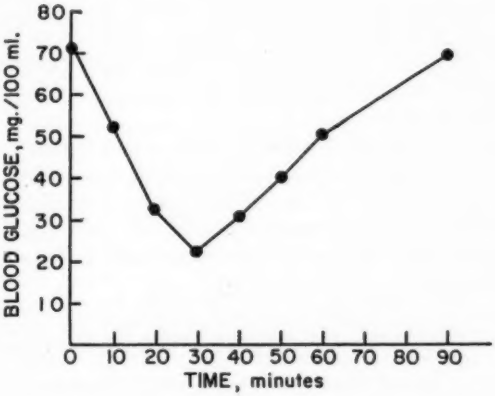

FIG. 2.—Normal intravenous insulin tolerance test.

Enforced Fast

A final procedure that is extremely useful in the differentiation of organic from functional hypoglycemia is the enforced fast. As has already been stated, functional hypoglycemia occurs in response to carbohydrate administration. In this condition, hypoglycemia does not occur on starvation. In contrast to this, organic hypoglycemia characteristically occurs on fasting. We have used a period of 24–36 hours of fasting with frequent sampling of venous blood glucose to determine whether or not this value is falling progressively during the fast. It sometimes is possible to predict that hypoglycemia will occur after fasting from the steady decrease in blood glucose concentration which occurs in the first few hours of fasting.

Some investigators, in addition, have added a period of heavy exercise to the fast to accelerate glucose removal and accentuate any downward trend of blood glucose levels. We have found this unnecessary, since the standard insulin tolerance test uniformly produces hypoglycemia and allows a measure of the response to hypoglycemia.

CLINICAL FEATURES OF SPECIFIC TYPES OF HYPOGLYCEMIA

Islet Cell Adenoma of Pancreas

This disease is characterized by progressive, recurrent symptoms of hypoglycemia. Attacks usually occur after periods of fasting and, initially, episodes may be noted only if the patient misses a meal. As the disorder progresses, symptoms become more severe and disorientation, bizarre behavior, personality change, convulsions and unconsciousness may occur. The patient rapidly learns that food intake will relieve his symptoms temporarily, and many patients with islet cell tumors gain weight rapidly due to excessive ingestion of carbohydrate-containing foods. Recent reports have indicated that some patients with islet cell tumors also have adenomas of the pituitary and/or parathyroids. This combination is rare, and when it occurs a hereditary pattern for the disease usually can be demonstrated in the patient's family. Despite the rarity

of the syndrome, it is important to realize that symptoms from an islet cell tumor may be masked by signs of pituitary tumor or hyperparathyroidism. In addition, careful follow-up of patients treated for islet cell tumors is necessary to demonstrate signs due to other benign adenomas, should they appear later.

CASE 1.—A 27-year-old Chinese student had been well until June, 1953 when he experienced the first of 3 episodes characterized by confusion, staggering and "grogginess" coming on when he failed to eat regularly. During the third episode, he became combative and was taken to his local hospital, where a blood glucose determination showed a value of 47 mg./100 ml. His symptoms subsided rapidly after he was given orange juice. Subsequently, during a period of enforced fasting, another episode of confusion and belligerency occurred and the blood glucose level was found to be 33 mg./100 ml. Surgical exploration was carried out, but no islet cell tumor was found. The terminal two thirds of the pancreas was resected. Despite this, the attacks recurred 1 week after operation. Histologic examination of the resected portion of the pancreas failed to reveal tumor, hyperplasia or hypertrophy of the islet cells. He was referred to the Clinical Center of the National Institutes of Health for further study. Physical examination was normal. The blood pressure was 138/80. There was no pigmentation. The heart was of normal size; the liver was barely palpable at the right costal margin. Neurologic examination was unremarkable.

Examination of the blood showed normal values for volume of packed red cells, white cell count and differential count. The urine was normal. Liver function tests and plasma 17-hydroxycorticosteroids were normal, as was the rise in plasma 17-hydroxycorticosteroids in response to intravenous ACTH.

The fasting blood glucose level ranged from 21 to 36 mg./100 ml. During a 24-hour fast, the blood glucose fell from a postprandial level of 72 mg./100 ml. to 29 mg./100 ml. at 22 hours, and he became confused and belligerant. After several days of high-carbohydrate feeding, an intravenous glucose tolerance test showed a prompt rise with rapid decrease to hypoglycemic levels. Hypoglycemia unresponsiveness was severe. An insulin tolerance test was carried out before lunch with 0.05 units of insulin per kg. body weight because of the known severe hypoglycemia on fasting. The blood glucose level fell from 70 to 20 mg/100 ml. Hypoglycemia unresponsiveness again was demonstrated. Neither epinephrine nor glucagon administration changed the blood

glucose level. The results of the intravenous glucose tolerance test and insulin tolerance test are shown in Figures 3 and 4.

Because he refused further surgery at this time, medical therapy with cortisone, 100 mg./24 hours, was instituted. On this regimen, the fasting blood glucose became normal, and further attacks of hypoglycemia did not occur until the dose of cortisone was reduced to 62.5 mg./24 hours. After cessation of steroid therapy, severe hypoglycemia recurred. Surgical exploration then was performed, and a 1 cm. tumor was removed from the uncinate lobe of the pancreas. The fasting blood glucose rose

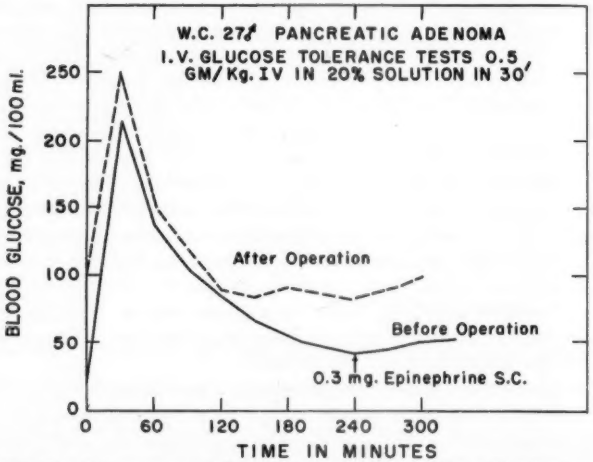

FIG. 3.—Intravenous glucose tolerance tests in islet cell adenoma of pancreas.

to 200 mg./100 ml. after surgery but was 80 mg./100 ml. 6 days postoperatively, and has remained normal thereafter. The intravenous glucose tolerance test, the insulin tolerance test, the fast test and the epinephrine test were repeated after surgery and all were normal. Some of these tests are included in Figures 3 and 4. It is of interest that hypoglycemia responsiveness was completely normal after operation. The patient remains well 4 years after surgery.

Comment: In this patient, the symptoms of hypoglycemia were those related to the central effects of glucose deficit. At no time did he complain of sweating, hunger or palpitation.

The differentiation between functional and organic hypoglycemia is especially well demonstrated in this case. Hypoglycemia unresponsive-

ness was severe and unremitting. In this instance, the defect in glycogenolysis was so severe that the blood glucose concentration failed to rise in response to either epinephrine or glucagon. This lack of response, however, is not found in all patients with islet cell adenoma. Other types of organic hypoglycemia were ruled out by the demonstration of normal hepatic, thyroid and adrenal function.

The efficacy of 17-hydroxycorticosteroid therapy in raising the blood glucose concentration is well demonstrated by the preceding case. In addition to its usefulness in patients with metastatic carcinoma of the islet cells and in patients who refuse surgery, some

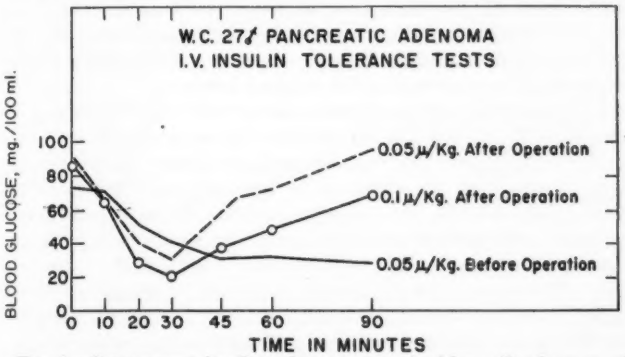

FIG. 4.—Intravenous insulin tolerance tests in islet cell adenoma of pancreas.

authors have suggested the use of 17-hydroxycorticosteroid therapy in the preoperative preparation of these patients for surgery (4, 10). These agents will prevent difficulties with hypoglycemia during the procedure and may prevent the occasional occurrence of fatal postoperative hyperpyrexia. Medical therapy of this type, however, is not curative, and the major treatment for this disorder is surgical.

At the time of surgical exploration of patients with islet cell tumors, certain precautions must be kept in mind. First, it must be recognized that the adenomas are multiple in some patients (13% in one series) (20), thus making complete extirpation difficult. Careful exploration, however, usually will lead to discovery of one or more adenomas and result in successful extirpation of the tumor tissue. Second, in those instances in which the tumor

is difficult to find, it should be remembered that about a quarter of the tumors are located in the head of the pancreas and that some of these will be in the uncinate lobe of the pancreas, posterior to the duodenum (11). Mobilization of the duodenum is necessary to locate the tumor if this is the case. Rarely, aberrant pancreatic tissue is the site of origin of islet cell adenomas. The most common locations of such extrapancreatic tumors are the splenic hilus, along the splenic vein and on the greater curvature of the stomach. The search must be extended to these areas if the tumor is not found in the pancreas itself. Only a small proportion of islet cell tumors are malignant. However, with carcinoma of the islets, regional and distant metastases occur and these retain the ability to secrete insulin. In such instances, the hypoglycemia is not relieved by removal of the primary tumor.

The incidence of hyperplasia of the islet cells is difficult to ascertain. When a tumor has not been found, many surgeons routinely have resected the distal two thirds of the pancreas in the hope of removing the tumor, or of removing enough hyperfunctioning islet cells to result in modification of the hypoglycemia. In some such specimens, hyperplastic islets have been seen, but the hypoglycemia has been relieved only in about half of the cases (11). The place of pancreatic resection in the therapy of this disorder, therefore, remains in question. Islet cell tumors rarely exceed 2 cm. in diameter, and many patients subjected to resection harbor a small tumor in the remaining pancreatic tissue.

Spontaneous Functional Hypoglycemia

This disorder is the most common clinical form of hypoglycemia. Its features, although quite different from those of the organic types of hypoglycemia, are equally characteristic. Symptoms of hypoglycemia occur repeatedly 1–3 hours after meals. The most common symptoms are those we have already described as being associated with rapid change in blood glucose level; i.e., sweating, hunger, palpitation and dizziness. Attacks do not occur on prolonged fasting. In contrast to episodes of organic hypoglycemia, the attacks of functional hypoglycemia are short-lived, since hypoglycemia responsiveness is normal in this disorder. Indeed, the period of hypoglycemia often is so transient that the patient may never have taken food to relieve the symptoms. The episodes of

hypoglycemia usually do not increase in severity with time. The history of recurrent, nonprogressive symptoms of hypoglycemia occurring *after* meals rather than in the morning before breakfast is suggestive of this diagnosis.

The pathogenesis of this type of hypoglycemia is not clear. Typically, the condition is encountered in tense persons with other manifestations of anxiety, but this is not always the case. A currently popular explanation for the episodes of hypoglycemia is that excessive secretion of insulin occurs in response to acute rises in blood glucose level due to the autonomic hyperactivity seen in anxiety states. Such an explanation fits well with the major clinical features of functional hypoglycemia and with the character of the glucose tolerance test in this disorder. Glucose tolerance tests in functional hypoglycemia frequently show exaggeration of all the physiologic phenomena of the normal glucose tolerance test, with higher peaks after glucose ingestion, more rapid and greater falls to the nadir and rapid response to the hypoglycemic blood glucose levels.

It has been pointed out, however, that many patients with functional hypoglycemia have associated organic disease of various kinds (13). These have included basal ganglia disorders such as parkinsonism, hypothyroidism, cholelithiasis, duodenal ulcer and helminthiasis. For this reason, some doubt has been cast on the specificity of the diagnosis of functional hypoglycemia, which is considered by some to be a relatively nonspecific symptom complex instead of a disease entity. The relationship of the associated diseases to the pathogenesis of the hypoglycemia is unknown.

Because hypoglycemia responsiveness is normal in these patients, it may be difficult to draw a blood sample during a spontaneous attack in time to demonstrate the association between hypoglycemia and the patient's symptoms. Since proof of the diagnosis rests on the demonstration of this association in the presence of normal hypoglycemia responsiveness, the clinical suspicion must be confirmed by the use of tests which produce hypoglycemia of a degree sufficient to produce symptoms and stimulate the response to hypoglycemia. The intravenous glucose tolerance test and the insulin tolerance test are most useful for this purpose. Enforced fasting yields little or no change in blood glucose levels throughout the 24-hour period.

CASE 2.—A 33-year-old woman had had occasional "spells' for 1 year. The first episode, which occurred 6 hours after the evening meal, was characterized by headache, nausea, palpitation, sweating and tachycardia. These symptoms lasted 15 minutes. The next day, similar episodes occurred 1 hour after breakfast and 3½ hours after supper. Her physician made the diagnosis of functional hypoglycemia and placed her on a high-protein, low-carbohydrate diet. On this regimen, she was symptom-free for 6 months. After that time, carbohydrate intake was increased without medical advice and the attacks recurred.

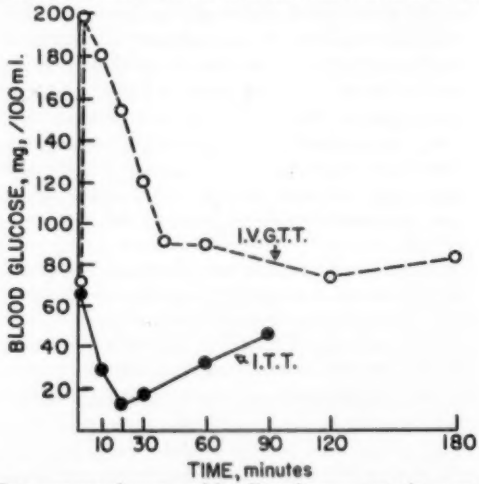

FIG. 5.—Intravenous glucose and insulin tolerance tests in spontaneous functional hypoglycemia.

Physical examination was normal. There were no signs of endocrine disease. All routine laboratory determinations were within normal limits. During an enforced 24-hour fast, little change in blood glucose level occurred, and she remained symptom-free. The intravenous glucose tolerance test, carried out with 25 Gm. glucose intravenously in a single injection, showed a prompt rise in blood glucose and a rapid fall to hypoglycemic levels. Her symptoms were reproduced in full while the blood glucose level was low. Hypoglycemia responsiveness was normal, and the symptoms subsided promptly as the blood glucose level rose. The insulin tolerance demonstrated the same findings. These tests are shown in Figure 5. Therapy with a high-protein, low-carbohydrate diet was reinstituted and the attacks ceased.

Comment: In this patient, the occurrence of typical attacks of hypoglycemia within a few hours after meals together with absence of attacks on fasting suggested the diagnosis of functional hypoglycemia. Production of hypoglycemia with the insulin and the glucose tolerance test reproduced her symptoms, and hypoglycemia responsiveness was normal. No evidence of organic disease was found by history, physical examination or laboratory studies.

The therapy of functional hypoglycemia is medical. Surgical exploration need not be carried out in these patients, since the tests of carbohydrate metabolism clearly demonstrate normal hypoglycemia responsiveness. Although psychiatric treatment may be indicated for associated anxiety symptoms, the major therapy for the hypoglycemia is dietary. In 1936, Conn and Newburgh demonstrated that protein meals result in practically no acute rise in blood glucose levels, while equivalent feedings of carbohydrate promptly raise the glucose values (9). Reasoning that functional hypoglycemia represented excessive insulin secretion in response to acute rises in blood glucose, these workers treated functional hypoglycemia with high-protein, low-carbohydrate diets. The dramatic results of this simple form of therapy are now well known. Typical diets include 120 Gm. protein, 80 Gm. carbohydrate and 90–110 Gm. fat, and are remarkably effective in preventing recurrent hypoglycemia.

The frequent occurrence of another form of spontaneous functional hypoglycemia has recently been emphasized (31). Seltzer *et al.* have reported 110 patients with mild diabetes mellitus, many of whom had hypoglycemia with symptoms in the absence of insulin therapy. Oral glucose tolerance tests in these patients revealed persistently elevated blood glucose values beyond 2 hours after glucose ingestion, with a slow fall to hypoglycemic levels subsequently. The mechanism of this change is unknown, but its frequency suggests that diabetes mellitus should be considered in any patient with functional hypoglycemia whose glucose tolerance test shows persistence of elevated values and a late fall to low blood glucose levels.

Hepatic Disease

Together with functional hypoglycemia and islet cell adenomas, hepatic disease has been considered one of the three most common

causes for hypoglycemia encountered in clinical practice. Hypoglycemic episodes have been reported to occur in various forms of liver disease including portal cirrhosis, carcinoma, hepatitis, chronic passive congestion and cholangitis. Data concerning the frequency of hypoglycemia in liver disease are difficult to obtain, but range from the reports of frequent occurrence of low blood glucose levels in such a mild hepatic disorder as the chronic passive congestion of congestive heart failure (26) to analyses of many patients with liver disease without encountering any but a rare case of hypoglycemia (37).

In our experience, the occurrence of symptomatic hypoglycemia in liver disease is rare. Except for occasional patients with terminal hepatic failure, the only instances in which we have observed this phenomenon have been in patients with liver disease complicated by small bowel disease, starvation or some other serious illness. Nevertheless, hypoglycemia of liver disease deserves consideration because (1) the diagnosis can be made by means of the simple clinical tests of carbohydrate metabolism outlined previously, (2) the mechanism of the hypoglycemia is fairly clear and (3) treatment of the hypoglycemic episode may prevent death in a patient who is destined to recover from his underlying hepatic disorder.

The clinical picture of hypoglycemia in liver disease does not differ from that of hypoglycemia in other circumstances. The symptoms may be those either of rapid or of slow onset of low blood glucose levels. If the patient has hepatic failure, it may be difficult to separate the central nervous system abnormalities of hypoglycemia from those of the basic disorder. It is necessary, therefore, to estimate the blood glucose level in such cases whenever the pathogenesis of the symptoms is unclear.

The glucose tolerance test is helpful in the diagnosis of hypoglycemia in hepatic disease. The curve shown in the case report of the patient with von Gierke's disease (Fig. 6) is typical of that found in other forms of liver disease. The blood glucose level rises rapidly after ingestion of glucose and then remains elevated. This elevation may last 1–3 hours, after which a rapid decline to hypoglycemic levels of blood glucose occurs. The insulin tolerance test shows hypoglycemia unresponsiveness. Therapy in this type of

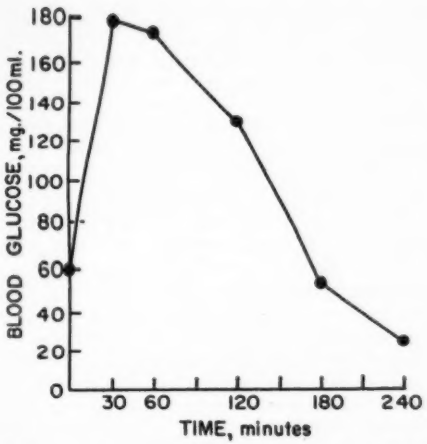

FIG. 6.—Oral glucose tolerance test in glycogenosis (von Gierke's disease).

hypoglycemia consists of a high-carbohydrate diet plus whatever measures are indicated for the underlying liver disease.

UNUSUAL CAUSES OF HYPOGLYCEMIA EXHIBITING SPECIAL FEATURES OF INTEREST

GLYCOGENOSIS (VON GIERKE'S DISEASE)

Glycogenosis represents a special variety of hepatic disease in which hypoglycemia is but one of several metabolic abnormalities due to a single specific enzymatic anomaly. The disease, in most instances, is due to absence of, or a marked decrease in, activity of glucose-6-phosphatase, an enzyme which governs a major step in the release of glucose from the liver to the blood stream. The lack of glucose-6-phosphatase is responsible for the hypoglycemia and the hypoglycemia unresponsiveness found in glycogenosis.

Other manifestations of this disorder include ketosis, poor growth, hepatomegaly and, occasionally, severe hyperlipemia.

CASE 3.—A 6-year-old boy entered the hospital with a history of poor growth and a protuberant abdomen of several years' duration.

He never had grown well. At age 2, a liver biopsy had shown numerous clear spaces tightly packed in liver cells; glycogen estimation was not done. At that time, the serum cholesterol was 620 mg./100 ml., total lipids, 4,236 mg./100 ml. There were no clinical symptoms of hypoglycemia.

Physical examination at age 6 showed dwarfism with normal proportions, lipemia retinalis and massive hepatomegaly. The fasting blood glucose was 15 and 40 mg./100 ml. Acetonuria was present. The serum cholesterol was 500 mg./100 ml.; bromsulfonphthalein retention, 36% in 45 minutes; thymol turbidity, 12 units; alkaline phosphatase, 13 Bodansky units.

The oral glucose tolerance test revealed a rapid rise with an abnormally elevated 2-hour value, followed by a rapid fall to hypoglycemic levels without response by 4 hours (Fig. 6). A galactose tolerance test was normal. The blood glucose did not rise in response to epinephrine.

Comment: In this case, hypoglycemia was an incidental finding. The patient never had symptoms which could be attributed to low blood glucose levels. However, the glucose tolerance test obtained here is typical of patients with hypoglycemia of hepatic disease with a high plateau of the blood glucose level followed by a rapid decrease to abnormally low levels. The occurrence of this type of curve in glycogenosis suggests that abnormality of end-organ response to fluctuations in blood glucose level may be the major reason for the occurrence of hypoglycemia in other forms of hepatic disease as well.

Hypoglycemia with Massive Tumors

Although isolated case reports of hypoglycemia in patients with massive tumors have appeared for years, many physicians are unaware of the occurrence of this interesting phenomenon. Patients with this type of hypoglycemia have all had massive tumors, usually of connective tissue origin. The tumors have weighed 1.5–10 kg. The hypoglycemia, in most instances, has been severe. Extensive study has failed to elucidate the mechanism for the hypoglycemia, and it is probable that more than one mechanism is operative in different patients.

Case 4.—A 47-year-old man had had multiple episodes of intestinal obstruction due to a sarcoma of the intestinal serosa (30). In the month before death, several episodes of dizziness occurred in the morning. For 3 days before admission, he consumed excessive amounts of candy. On the day of admission, a generalized clonic seizure occurred and he was admitted to the hospital in coma. Physical examination

showed emaciation, massive hepatosplenomegaly and multiple nodular masses in the midabdomen. The blood glucose was 9 and 18 mg./100 ml. on two occasions, and consciousness rapidly returned when intravenous glucose was given.

Liver function tests and plasma 17-hydroxycorticosteroids were normal. Recurrent hypoglycemia made massive glucose infusions necessary. The patient died on the 5th hospital day. Autopsy revealed a 0.5–1 cm. thick, white tumor completely enveloping the bowel, liver and spleen. The organs themselves were not involved, and there were no distant metastases. Microscopic examination of the liver, adrenals and pancreas was normal. The histologic diagnosis of the tumor was mesothelial cell sarcoma.

Extensive studies failed to demonstrate insulin-like activity in the tumor. It was not possible to demonstrate abnormalities of insulinase, abnormal amino acids in the tumor or urine or noninsulin hypoglycemia-producing materials in the tumor. The tumor levels of glycogen and amino acids were extremely high and the hypoglycemia was attributed to excessive glucose consumption and storage by the tumor.

Comment: The special interest which patients such as this engender stems from the fact that studies of hypoglycemia in these circumstances reveal basic mechanisms applicable to the occurrence of low blood glucose in other circumstances. Initially, it was postulated that the tumor must secrete an insulin-like substance. In actuality, of the 6 patients in whom studies of this possible explanation have been made, such activity has been found in only 1, a woman who had a 1,300 Gm. thoracic fibrosarcoma (2). In the present case, the evidence suggested that the tumor was utilizing glucose for energy and for amino acid synthesis at such a rapid rate that hypoglycemia occurred. This case would represent, then, an instance of excessive utilization of glucose by a specific peripheral tissue as a cause of the hypoglycemia.

Idiopathic Hypoglycemosis

This interesting disorder is one of the more common causes for hypoglycemia in children. The disease is genetically determined and occurs in infants and young children. The age of onset is usually before 1 year, and may be as early as 1–2 months. The disorder is characterized by repeated episodes of hypoglycemia, with hypoglycemia unresponsiveness. The severity varies, but may be of such a nature as to lead to permanent central nervous system damage. It is of interest that the hypoglycemic episodes become less frequent and may disappear as the child gets older.

The pathogenesis of the disease is unknown. In one autopsied case, examination of the pancreas showed marked diminution in the α-cells of the islets of Langerhans (25). Since these cells are the presumed site of origin of glucagon, it was postulated that idiopathic hypoglycemosis was due to an inherited deficiency of α-cells. Subsequent studies, however, have not borne out this hypothesis, and the cause of the hypoglycemia remains in doubt.

Since idiopathic hypoglycemosis is a self-limited disorder, treatment is medical and pancreatic surgery should be avoided. Fortunately, the advent of readily available preparations of adrenocorticotropic hormone and of cortisone, hydrocortisone and their derivatives has provided a satisfactory form of therapy. Moderate doses of ACTH or adrenal steroids completely eliminate the hypoglycemia.

HYPOGLYCEMIA DUE TO INGESTION OF NATURAL AND SYNTHETIC SUBSTANCES

Until now, this presentation has been concerned with spontaneous hypoglycemia. There are, however, some interesting clinical situations in which hypoglycemia occurs secondary to the ingestion of exogenous toxic materials. Some of these are seen frequently in certain indigent populations; others are restricted to certain geographic locations. In addition, the recent advances in the use of oral drugs for the treatment of diabetes mellitus have led to an increased general awareness of drugs capable of producing hypoglycemia. A few of these interesting materials are considered briefly here.

Hypoglycemia Due to "Smoke" Ingestion

It is well known that patients suffering from severe chronic alcoholism will drink intoxicating substitutes for ethanolic beverages if these substitutes are all that is available to them. Included among such materials are methanol, methanol antifreeze, isopropyl alcohol and various organic solvent mixtures containing mixtures of ethanol, methanol, ethyl acetate and other materials. Hypoglycemia does not occur as a feature of methanol or isopropyl alcohol poisoning, but is a major clinical manifestation of poisoning with organic solvent mixtures. Since these materials usually

are ingested in water, with which they make a smoky mixture, this syndrome has been called "smoke" poisoning (5).

Patients with "smoke" intoxication do not experience the symptoms associated with rapid decrease in blood glucose level. It is not known whether this is due to a slow fall in blood glucose or to the masking of these symptoms by those of alcoholic intoxication. Most patients become comatose within several hours after drinking the toxic mixture, and are admitted to the hospital with various nonspecific neurologic signs. The hypoglycemia responds rapidly to glucose infusion and does not recur. The pathogenesis of the hypoglycemia is unknown. Administration of "smoke" mixtures to animals does not alter blood glucose levels. The poor nutritional state of chronic alcoholics has suggested the possibility that starvation leading to depletion of liver glycogen is a contributory cause for hypoglycemia in these patients, but there is no evidence to substantiate such a theory.

The recognition of hypoglycemia in "smoke" drinkers depends on an awareness that nonspecific neurologic findings can be due to hypoglycemia. When a chronic alcoholic patient develops coma, the possibility of poisoning with intoxicating beverages other than ethanol must be considered, and the blood glucose level measured. Treatment consists only of glucose administration and supportive care.

Vomiting Sickness of Jamaica

For many years, children of the native groups of Jamaica have been observed to develop an acute illness characterized by abrupt vomiting and weakness, followed in many instances by coma and death. Although many observers have doubted that "vomiting sickness" is a specific clinical entity, others have attributed the illness to the ingestion of a fruit of the Blighia sapida tree, the "ackee." Recently, it was shown that this disorder is characterized by acute, severe hypoglycemia (35). Recognition of low blood glucose levels in patients with "vomiting sickness" has led to renewed interest in this disease and to studies of "ackee." Two polypeptide materials capable of producing severe hypoglycemia and vomiting in animals now have been isolated from the "ackee" seed (19). Studies in various species of animals revealed that these polypeptides result in severe depletion of liver glycogen and

prompt hypoglycemia (6). Patients with "vomiting sickness" subjected to liver biopsy, or examined at autopsy, have shown depletion of liver glycogen. The mechanism of action of these polypeptides is unknown.

Poisoning from the "ackee" is a public health problem peculiar to Jamaica. Interest in this disorder is widespread, however, because of the possibilities of finding other naturally occurring hypoglycemia-producing substances which might be used in the treatment of diabetes. Although other plant substances have modest hypoglycemic properties, as yet none has been found to be as potent as that from the "ackee" seed and none is of use in human therapy.

Other substances, however, do have hypoglycemic action in man, with less toxicity than do these naturally occuring plant materials. The major compounds of current clinical interest are of two general types, sulfonylureas and derivatives of guanidine.

The Sulfonylureas

In the course of therapeutic trials of new sulfonamide drugs, it was noted that some of the patients receiving one of them had central nervous system symptoms consisting of somnolence, tremulousness and hunger. It was noted that the blood glucose level was low in these patients. Subsequent studies revealed that this material, 1-butyl-3-p-aminobenzene-sulfonylurea, regularly produced hypoglycemia in normal and in some diabetic subjects. This compound, known as carbutamide, and a related material, tolbutamide (1-butyl-3-p-tolysulfonylurea), have been subjected to extensive clinical and experimental study. Tolbutamide now is in general clinical use in the therapy of diabetes mellitus.

Tolbutamide does not produce clinical symptoms of hypoglycemia in man unless administered with alkali or to patients also receiving insulin. However, either compound produces a prompt lowering of the blood glucose level in normal subjects, the lowest levels being reached 1–2 hours after oral ingestion. The hypoglycemia may persist as long as 6 hours. From the standpoint of the mechanism of action of the sulfonylureas, it is of interest that these compounds are inactive in the absence of the pancreas. Although considerable difference of opinion persists, the best

evidence suggests that sulfonylureas produce hypoglycemia by stimulating the islets of Langerhans to secrete insulin. Differences in the metabolic effects between small doses of insulin and sulfonylureas probably can be attributed to the fact that intraportal insulin produces effects different from those seen after peripheral administration of insulin. The effects of tolbutamide parallel closely those of small doses of intraportal insulin, suggesting that stimulation of insulin secretion is the major action of this drug. For this reason, sulfonylureas are ineffective in diabetes due to absolute insulin deficiency, but are helpful in the treatment of mild diabetes in patients who may have partial if not normal islet cell function.

Guanidines

Decamethylene diguanidine (Synthalin A) was among the earliest compounds found to produce hypoglycemia after oral administration. Clinical interest in this compound was limited, however, when it was shown that the hypoglycemia was accompanied by hepatic damage and depletion of liver glycogen. With the recent interest in oral hypoglycemic agents, however, the guanidine compounds have been restudied and three have shown promise in clinical trials in diabetic patients (28). These are phenethylbiguanide, amylbiguanide and isoamylbiguanide. These materials, in contrast to sulfonylureas, produce hypoglycemia in the presence or absence of the pancreas and, therefore, do not require the presence of insulin-secreting cells. The mechanism of action presumably relates to the inhibitory action of these materials on the cytochrome system, but this is not certain. Although side effects limit the general clinical application of the biguanides, their effectiveness in the absence of the pancreas makes them potentially valuable agents in the treatment of patients with insulin-resistant diabetes mellitus.

SUMMARY

1. In the study of the patient with hypoglycemia, consideration of the physiologic mechanisms which may produce low blood

glucose levels is of help in the differential diagnosis of the cause of the hypoglycemia.

2. Hypoglycemia is a symptom, not a disease, and the detection of low blood glucose levels is an urgent indication for investigation of the cause of the low blood glucose level.

3. The organic hypoglycemias are characterized by prolonged, progressively severe hypoglycemic episodes of slow onset while fasting, with hypoglycemia unresponsiveness.

4. The functional hypoglycemias are characterized by brief, nonprogressive hypoglycemia occuring after meals. Hypoglycemia responsiveness is normal.

5. Painstaking use of oral and intravenous glucose tolerance tests, the intravenous insulin tolerance test and prolonged fasts aid in the differential diagnosis of hypoglycemia.

6. New causes of hypoglycemia continue to be recognized. Careful study of these types of hypoglycemia has yielded information of physiologic, diagnostic and therapeutic importance. Some of these types of hypoglycemia have been described briefly.

REFERENCES

1. Ashmore, J., Haistings, A. B., and Nesbett, F. B.: Studies on carbohydrate metabolism in the rat, J. Biol. Chem. 218:77, 1956.
2. August, J. T., and Hiatt, H. H.: Severe hypoglycemia secondary to a non-pancreatic fibrosarcoma with insulin activity, New England J. Med. 258:17, 1958.
3. Bearn, A. G., Billing, B. H., and Sherlock, S.: Response of the liver to insulin: Hepatic vein catheter studies in man, Ciba Found. Coll. Endocrinol. 6:250, 1953.
4. Brown, H., Hargreaves, H. P., and Tyler, F. H.: Islet cell adenoma of the pancreas: Metabolic studies on a patient treated with corticotropin and cortisone, A.M.A. Arch. Int. Med. 89:951, 1952.
5. Brown, T. McP., and Harvey, A. M.: Spontaneous hypoglycemia in "smoke" drinkers, J.A.M.A. 117:12, 1941.
6. Chen, K. K., *et al.*: Pharmacologic action of hypoglycin A and B, J. Pharmacol. & Exper. Therap. 121:272, 1957.
7. Christophe, J., and Mayer, J.: Effect of exercise on glucose uptake in rats and man, J. Appl. Physiol. 13:229, 1958.
8. Cochrane, W. A., *et al.*: Familial hypoglycemia precipitated by amino acids, J. Clin. Invest. 35:411, 1956.
9. Conn, J. W., and Newburgh, L. H.: The glycemic response to isoglucogenic quantities of protein and carbohydrate, J. Clin. Invest. 15:665, 1936.

10. Conn, J. W., and Seltzer, H. S.: Spontaneous hypoglycemia, Am. J. Med. 19:460, 1955.
11. Crain, E. L., Jr., and Thorn, G. W.: Functioning pancreatic islet cell adenomas, Medicine 28:427, 1949.
12. Elrick, H., Hlad, C. J., Jr., and Witten, T.: The enhancement of peripheral glucose utilization by glucagon, J. Clin. Invest. 34:1830, 1955.
13. Fabrykant, M.: The problem of functional hyperinsulinism or functional hypoglycemia attributed to nervous causes. I. Laboratory and clinical correlations, Metabolism 4:469, 1955.
14. Folin, O.: Two revised copper methods for blood sugar determinations, J. Biol. Chem. 82:83, 1929.
15. Fraser, R. W., Albright, F., and Smith, P. H.: Value of glucose tolerance test, insulin tolerance test, and glucose-insulin tolerance test in diagnosis of endocrinologic disorders of glucose metabolism, J. Clin. Endocrinol. 1:234, 1941.
16. Frawley, T. F.: The role of the adrenal cortex in glucose and pyruvic acid metabolism in man including the use of intravenous hydrocortisone in acute hypoglycemia, Ann. New York Acad. Sc. 61:464, 1955.
17. Goldstein, M. S., *et al.*: Action of muscular work on transfer of sugars across cell barriers: Comparison with insulin, Am. J. Physiol. 173:212, 1953.
18. Harris, S.: Hyperinsulinism and dysinsulinism, J.A.M.A. 83:729, 1924.
19. Hassall, C. H., and Reyle, K.: Hypoglycin A and B: Biologically active polypeptides from Blighia sapida, Nature 173:356, 1954.
20. Howard, J. M., Moss, N. H., and Rhoads, J. E.: Hyperinsulinism and islet cell tumors of the pancreas, Internat. Abst. Surg. 90:417, 1950.
21. Keys, A., *et al.*: *The Biology of Human Starvation* (Minneapolis: University of Minnesota Press, 1950), vol. I, pp. 538-579.
22. Lazarus, S. S., and Volk, B. W.: Studies on hypoglycemia responsiveness, Metabolism 2:500, 1953.
23. Levine, R., *et al.*: Action of insulin on the "permeability" of cells to free hexoses as studies by its effect on the distribution of galactose, Am. J. Physiol. 163:70, 1950.
24. Madison, L. L., and Unger, R.: The physiologic significance of the secretion of endogenous insulin into the portal circulation. I. Comparison of the effects of glucagon free insulin administered via the portal vein and via a peripheral vein on the magnitude of hypoglycemia and peripheral glucose utilization, J. Clin. Invest. 37:631, 1958.
25. McQuarrie, I., *et al.*: The metabolic and clinical effects of pituitary adrenocorticotropic hormone in spontaneous hypoglycemosis, *Proceedings of the First Clinical ACTH Conference* (Philadelphia: The Blakiston Company, 1950).
26. Mellinkoff, S. M., and Tumulty, P. A.: Hepatic hypoglycemia: Its occurrence in congestive heart failure, New England J. Med. 247:745, 1952.

27. Nelson, N.: A photometric adaptation of the Somogyi method for the determination of glucose, J. Biol. Chem. 153:374, 1944.
28. Odell, W. D., *et al.*: Phenethyl- amyl- and isoamybiguanide in the treatment of diabetes mellitus, A.M.A. Arch. Int. Med. 102:520, 1958.
29. Park, C. R., *et al.*: The transport of glucose and other sugars across cell membranes and the effect of insulin. Internal secretion of the pancreas, Ciba Found. Coll. Endocrinol. 9:240, 1956.
30. Sellman, J. C., *et al.*: Hypoglycemia associated with massive intra-abdominal mesothelial cell sarcoma, New England J. Med. (in press).
31. Seltzer, H. S., Fajans, S. S., and Conn, J. W.: Spontaneous hypoglycemia as an early manifestation of diabetes mellitus, Diabetes 5-437, 1956.
32. Silverstone, F. A., *et al.*: Age differences in the intravenous glucose tolerance test and the response to insulin, J. Clin. Invest. 36:504, 1957.
33. Somogyi, M.: Mechanism of epinephrine hyperglycemia, Endocrinology 49:774, 1951.
34. Stadie, W. C., Haugaard, N., and Vaughn, M.: The chemical combination of insulin with muscle (diaphragm) of normal rat, Am. J. M. Sc. 218:265, 1949.
35. Stuart, K. L., Jelliffe, D. B., and Hill, K. R.: Acute toxic hypoglycemia occurring in vomiting sickness of Jamaica (clinical aspects), J. Trop. Pediat. 1:69, 1955.
36. Sutherland, E. W., and Cori, C. F.: Effect of hyperglycemia glycogenolytic factor and epinephrine on liver phosphorylase, J. Biol. Chem. 188:531, 1951.
37. Zimmerman, H. J., Thomas, L. J., and Sherr, E. H.: Fasting blood sugar in hepatic disease with reference to infrequency of hypoglycemia, A.M.A. Arch. Int. Med. 91:577, 1953.

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